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Metal-Free, One-Pot, Sequential Protocol for Transforming α,β-Epoxy Ketones to β-Hydroxy Ketones and α-Methylene Ketones

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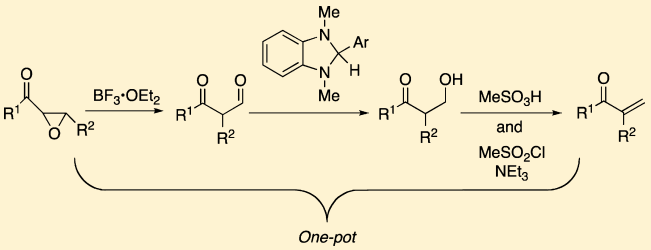
Supporting Information

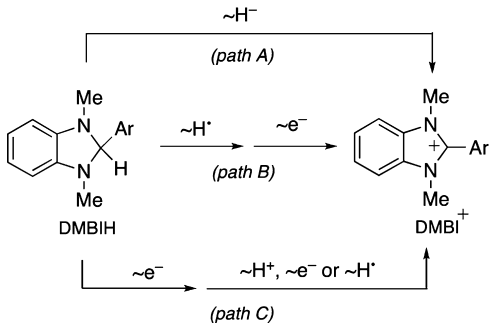
ABSTRACT: A new sequential, one-pot protocol for transforming 1,3-disubstituted 2,3-epoxy ketones to β-hydroxy ketones and α-methylene ketones has been developed. Reaction of epoxy ketones with boron trifluoride etherate (BF_3·OEt_2) generates the cationic intermediates by regioselective epoxide ring opening and an acyl shift. Then, a treatment of these cations with 2-aryl-1,3-dimethylbenzimidazolines (DMBIH) results in formation of 1,2-disubstituted 3-hydroxy ketones. DMBIH serves as a hydride donor in the second step of this process. Finally, the β-hydroxy ketones can be converted to 1,2-disubstituted 2-methylene ketones by treatment with methanesulfonic acid or a combination of methanesulfonyl chloride and triethylamine. Importantly, the sequential steps involved in formation of the α-methylene ketone products can be carried out in one pot.



INTRODUCTION

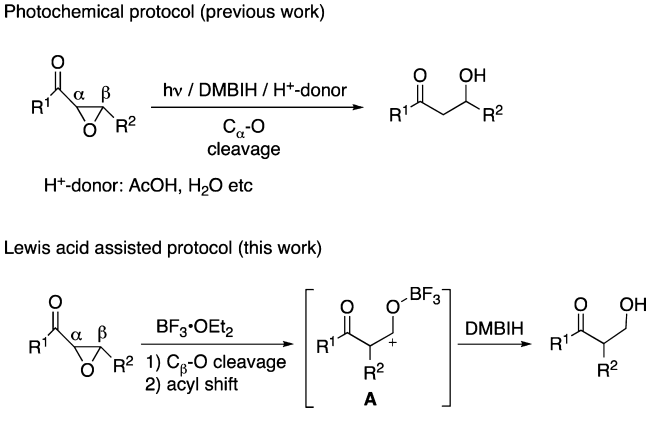
2-Aryl-1,3-dimethylbenzimidazolines (DMBIHs) act as efficient hydride, hydrogen atom, and electron donors (Scheme 1).[1] For example, DMBIH derivatives donate hydrides to carbocations[2] formed by Lewis acid complexation with certain Lewis basic substrates as well as cationic salts derived from nitrogen heterocycles (path A).[3] Recently, it was shown that DMBIHs donate hydride to benzhydrylium ions more efficiently than do NADH analogues.[4] In addition, hydrogen gas evolution from DMBIH derivatives takes place upon treatment with certain Brønsted–Lowry acids.[5] In thermal[6] or photochemical[7,8] processes, DMBIHs can act as effective reducing reagents for various organic functional groups. The DMBIH-promoted reactions are initiated by hydrogen atom abstraction (path B) or single electron transfer (SET) (path C). In the latter pathway, SET is followed either by sequential proton and SET or by hydrogen atom transfer. Finally, DMBIH derivatives have been utilized recently in artificial photosynthesis systems[9] as well as in organic semiconductor devices.[10]

Scheme 1. Pathways for Oxidation of 2-Aryl-1,3-dimethylbenzimidazoline (DMBIH)



In previous studies, we have shown that photoinduced electron transfer (PET) reactions of α,β-epoxy ketones in the presence of DMBIH derivatives produce β-hydroxy ketones. We have optimized this process to make it an efficient synthetic method (Scheme 2).[7a−d,f,g] House and others observed much earlier that boron trifluoride etherates such as BF_3·OEt_2 promote rearrangement reactions of α,β-epoxy ketones to form β-keto aldehydes through a mechanistic pathway involving regioselective epoxide ring opening followed by an acyl

Scheme 2. Photochemical and BF_3·OEt_2 Promoted Transformations of α,β-Epoxy Ketones to Isomeric β-Hydroxy Ketones



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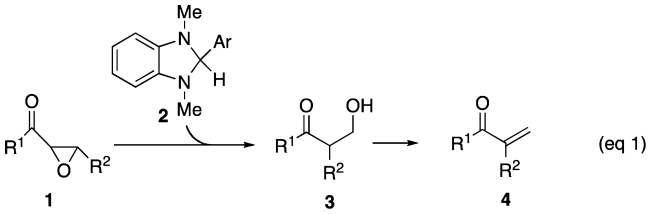
shift.[11−14] Previous investigations have demonstrated that DMBIH is compatible with conditions employed in processes promoted by several metal-containing Lewis acids such as $AlCl_3$, $ZnCl_2$, $SnCl_4$, and $FeCl_3$.[2] To our knowledge, reactions in which $BF_3{\cdot}OEt_2$ and DMBIH are simultaneously utilized as reagents have not been explored. We reasoned that, if these reagents were compatible, isomeric β-hydroxy ketones,[15] generated from α,β-epoxy ketones in the photochemical protocol, would be formed in $BF_3{\cdot}OEt_2$ promoted reactions of epoxy ketones if the expected carbocation intermediate **A** (Scheme 2) is trapped by hydride transfer from DMBIH. In this event, the process would represent a new, one-pot procedure for transforming α,β-epoxy ketones to β-hydroxy ketones. In the effort described below, which was designed to explore this proposal, we investigated reactions of variously substituted α,β-epoxy ketones **1** in the presence of $BF_3{\cdot}OEt_2$ and DMBIH derivatives **2** that form β-hydroxy ketones **3** and probed a one-pot method to convert α,β-epoxy ketones **1** to α-methylene ketones **4** (eq 1).



(eq 1)

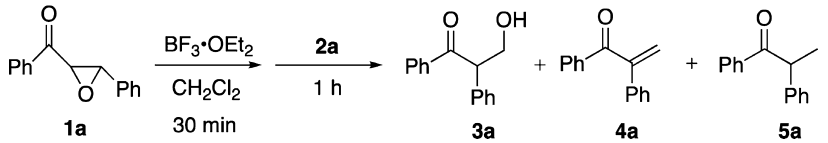
RESULTS AND DISCUSSION

In the initial phase of this effort, we observed that reaction of epoxy ketone **1a** ($R^1 = R^2$ = Ph; 0.50 mmol) with DMBIH **2a** (Ar = Ph; 1.5 equiv) in the presence of $BF_3{\cdot}OEt_2$ (1.1 equiv) in CH_2Cl_2 (1.5 mL) for 1 h leads to low-yielding (17%) formation of the expected hydroxyl ketone **3a**. The procedure used for this process was modified in an attempt to uncover conditions that would enable more efficient trapping of the putative, in situ formed carbocation intermediate by hydride transfer from **2a**. Consequently, **1a** was first treated with $BF_3{\cdot}OEt_2$ for 30 min and the resulting mixture was treated with **2a** for an additional 1 h (Table 1). By using this two-step, one-pot protocol, **3a** was produced in a yield of 39% along with enone **4a** and ketone **5a** (entry 1). While increasing the time of the hydride transfer reaction to 6 h at room temperature does not alter product yields (entry 2), heating to ca. 40 °C for 24 h leads to a significant decrease in the yield of **3a** (4%) and a corresponding increase in the yield of **4a** (30%) (entry 3). In addition, use of slightly more than a stoichiometric amount of $BF_3{\cdot}OEt_2$ and an excess of **2a** leads to a significantly improved yield of **3a** (entries 6 and 8). Notably, the influence of heating for 24 h on the product yields in the reactions using these quantities of the Lewis acid and hydride donor is marginal (compare entries 7 and 6), an observation that markedly contrasts with the effect of temperature when an excess of $BF_3{\cdot}OEt_2$ is used (compare entries 3 and 1). Finally, **3a** is generated in slightly lower yields when less than stoichiometric amounts of $BF_3{\cdot}OEt_2$ are employed for this process (entries 9 and 10).

The utilization of other hydride donors in this process was probed briefly. The $BF_3{\cdot}OEt_2$ promoted reaction of **1a**, employing 2,6-dimethyl-3,5-pyridinedicarboxylate (Hantzsch ester)[16] as the reducing agent, was observed to generate **3a** in 28% yield along with **4a** (4%) and β-keto aldehyde **7a** (17%). In contrast, hydrosilanes such as Ph_3SiH and Et_3SiH are not effective in promoting the formation of **3a**. In these cases, ^1H NMR analysis of the reaction mixtures revealed that **7a** is produced in near-quantitative yields. These observations are consistent with the expected order of hydride-donating ability of Hantzsch esters and hydrosilanes versus DMBIH.[4] This exploratory study enabled us to define optimal conditions (1.1 equiv of $BF_3{\cdot}OEt_2$, 1.5 equiv of **2a**, room temperature, 1.5 h) for the transformation of epoxy ketone **1a** to hydroxy ketone **3a** (entry 6 in Table 1).[17]

The results of further studies reveal that treatment of β-keto aldehyde **7a** with $BF_3{\cdot}OEt_2$ and **2a** leads to the formation of **3a**−**5a** in yields that are similar to those obtained in the reaction of **1a** (eq 2). This observation demonstrates that BF_3 coordination with the aldehyde oxygen in **7a** is important in causing hydride transfer reduction by **2a**. We also explored the use of $NaBH_4$ to reduce **7a** (0.20 mmol, 2.0 mL MeOH, 2 h) (eq 3). When 1.0 equiv of $NaBH_4$ is used in this reaction, the

Table 1. Sequential Reactions of Epoxy Ketone 1a with $BF_3{\cdot}OEt_2$ and DMBIH 2a[a]



entry	$BF_3{\cdot}OEt_2$ (equiv vs **1a**)	**2a** (equiv vs **1a**)	yield (%) **3a**[b]	**4a**[c]	**5a**[c]
1	1.5	1.2	39	13	7
2[d]	1.5	1.2	40	12	7
3[e]	1.5	1.0	4	30	4
4	1.1	1.0	37	16	7
5	1.1	1.2	61	7	5
6	1.1	1.5	74	1	1
7[e]	1.1	1.5	65	2	3
8	1.1	2.0	73	5	1
9	0.3	1.0	49	1	0
10	0.3	1.5	62	0	0

[a]Conditions unless noted otherwise: **1a** (0.50 mmol), CH_2Cl_2 (1.4−1.5 mL), room temperature, 1.5 h reaction time. [b]Isolated yield. [c]Determined by using ^1H NMR. [d]After addition of **2a**, 6 h at room temperature. [e]After addition of **2a**, 24 h at ca. 40 °C.

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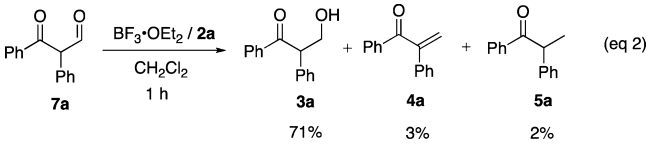
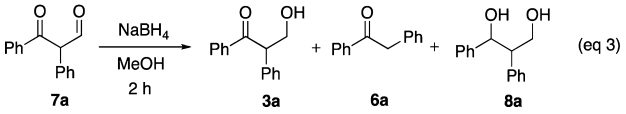




fully reduced diol **8a** (33%) is formed along with small amounts of **3a** (4%) and **6a** (22%). Utilization of lesser amounts of $NaBH_4$ does not result in an improvement in the yield of **3a** (0.5 equiv of $NaBH_4$ gives 11% of **3a** and 49% of **6a** at 88% conversion, and 0.25 equiv of $NaBH_4$ gives 3% of **3a** and 33% of **6a** at 71% conversion).

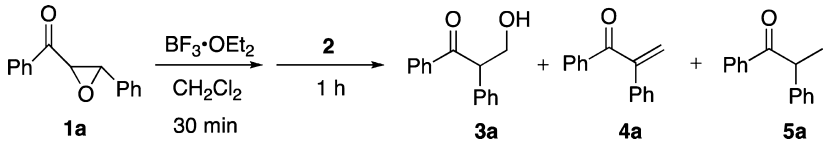
The effect of arene ring substituents in the DMBIHs **2** (Table 2) on the efficiencies of the BF_3·OEt_2 induced reaction of epoxy ketone **1a** was explored next. With the exception of **2f** (Ar = *o*-HOC_6H_4), most of the DMBIHs (1.5 equiv) explored in this study promoted the reduction step in the reaction to produce **3a** in good yields (>67%). In a manner that is consistent with the reaction induced by **2a**, a decrease in the amount of **2d** (Ar = *p*-$MeOC_6H_4$) to 1.0 equiv causes the yield of **3a** to drop to 56% concurrent with a corresponding increase in the yields of **4a** (9%) and **5a** (2%). In addition, the reaction promoted by **2f** (Ar = *o*-HOC_6H_4) forms **3a** in a low yield and **7a** in a significant quantity (entry 6). In contrast, the regioisomer **2e** (Ar = *p*-HOC_6H_4) is as effective as **2a** (entry 5) in promoting this reaction. It should also be noted that the reaction using **2e** for 24 h at elevated temperature produces **3a** in 71% yield, which is higher than that observed for the **2a** induced process (entry 7 in Table 1). While the difference in yield of **3a** between the reactions promoted by **2b** (Ar = *p*-ClC_6H_4) and **2c** (Ar = *o*-ClC_6H_4) is small (entries 2 and 3), the efficiency of the reaction induced by **2e** is much greater than that by **2f** (entries 5 and 6). This observation suggests that a steric effect of the ortho arene substituent **2** is not significant. It has been reported that an intramolecular hydrogen-bonding interaction exists between *o*-OH and the nitrogen lone pair in **2f**.[1,5a,18] It is possible that this specific interaction causes hydride transfer from **2f**, which generates the corresponding imidazolium ion ($DMBI^+$), to be slow.

In the final phase of this investigation, applications of the developed protocol to reactions of aryl ring substituted epoxy ketones **1a**–**h** were probed (Table 3). In each case, the corresponding hydroxyl ketone **3** is produced in modest to high yield (63–85%). Notably, the benzalacetone derived epoxy ketone **1i** also participates in this sequential reaction to form **3i** (62%) as a major product (entry 9).[19]

Plausible reaction pathways for the conversion of epoxy ketone **1** to the observed products **3**–**6** are displayed in Scheme 3. In this process, BF_3·OEt_2 coordination to **1** promotes regioselective epoxide ring opening of the intermediate **9** to form the cation **10**, which then undergoes an acyl shift to generate the BF_3 coordinated keto aldehyde **11**, which is in equilibrium with **7**. Hydride transfer from **2** to **11** subsequently gives alkoxy borinate **12**, which is transformed to hydroxyl ketone **3** by hydrolysis during workup. One possible route for formation of unsaturated ketone **4** involves complexation of BF_3·OEt_2 with **12** to give **13**, which loses a proton to form the BF_3 enolate **14**. Enolate **14** could simply undergo concerted loss of BF_3 and the borinic acid $HOBF_3$ to produce **4** or a stepwise process through allyl cation **15** to form **4**. Finally, a hydride transfer reaction between cation **15** and **2** would produce alkoxide **16**, the precursor of **5**. Compound **6** is probably formed by retro-aldol type fragmentation of **12** via the enolate **17**. These mechanistic proposals are consistent with the observations that the use of larger quantities of BF_3·OEt_2 leads to an increased yield of **4** (see entries 1–3 in Table 1) while an increase in the amount of **2** enhances the formation of **3** (see entries 4–6 and 8 in Table 1).

Because α-methylene ketones are attractive synthetic building blocks,[20] we have probed the conditions for transforming hydroxyl ketones **3** to unsaturated ketones **4**. Two approaches, involving Brønsted–Lowry acid and base promoted sequential sulfonylation–elimination, were considered for this purpose. The results of exploratory studies demonstrated that an ideal acid promoted process involves treatment of **3a** (0.50 mmol) with $MeSO_3H$ (1.0 equiv) in CH_2Cl_2 (1.5 mL) at ca. 40 °C for 5 h.[21] This reaction generates **4a** in 74% yield along with a trace quantity of recovered **3a** (upper path in Scheme 4). In addition, we found that $MeSO_2Cl$ (1.3 equiv) and NEt_3 (6.1 equiv)[22] are ideal for converting **3a** (0.20 mmol,

Table 2. Reactions of Epoxy Ketone 1a with BF_3·OEt_2 and Various DMBIHs 2[a]



		yield (%)		
entry	2 (Ar)	3a[b]	4a[c]	5a[c]
1[d]	**2a** (Ph)	74	1	1
2	**2b** (*p*-ClC_6H_4)	67	4	0
3[e]	**2c** (*o*-ClC_6H_4)	68	6	1
4[e]	**2d** (*p*-$MeOC_6H_4$)	69	5	1
5[e]	**2e** (*p*-HOC_6H_4)	75	3	2
6[f]	**2f** (*o*-HOC_6H_4)	21	13	0

[a]Conditions: **1a** (0.50 mmol), BF_3·OEt_2 (1.1 equiv), **2** (1.5 equiv), CH_2Cl_2 (1.5 mL), room temperature, 1.5 h reaction time. [b]Isolated yield. [c]Determined by using ^1H NMR. [d]Same as entry 6 in Table 1. [e]Small amounts of 1,2-diphenylethanone were obtained: ca. 1% for entry 3, trace for entry 4, ca. 5% for entry 5. [f]**7a** (64%) was obtained.

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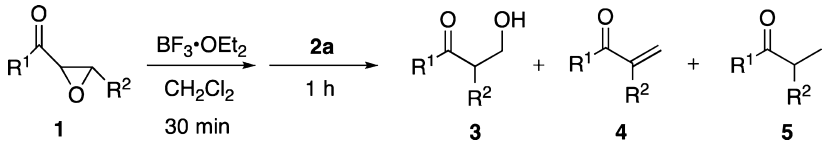
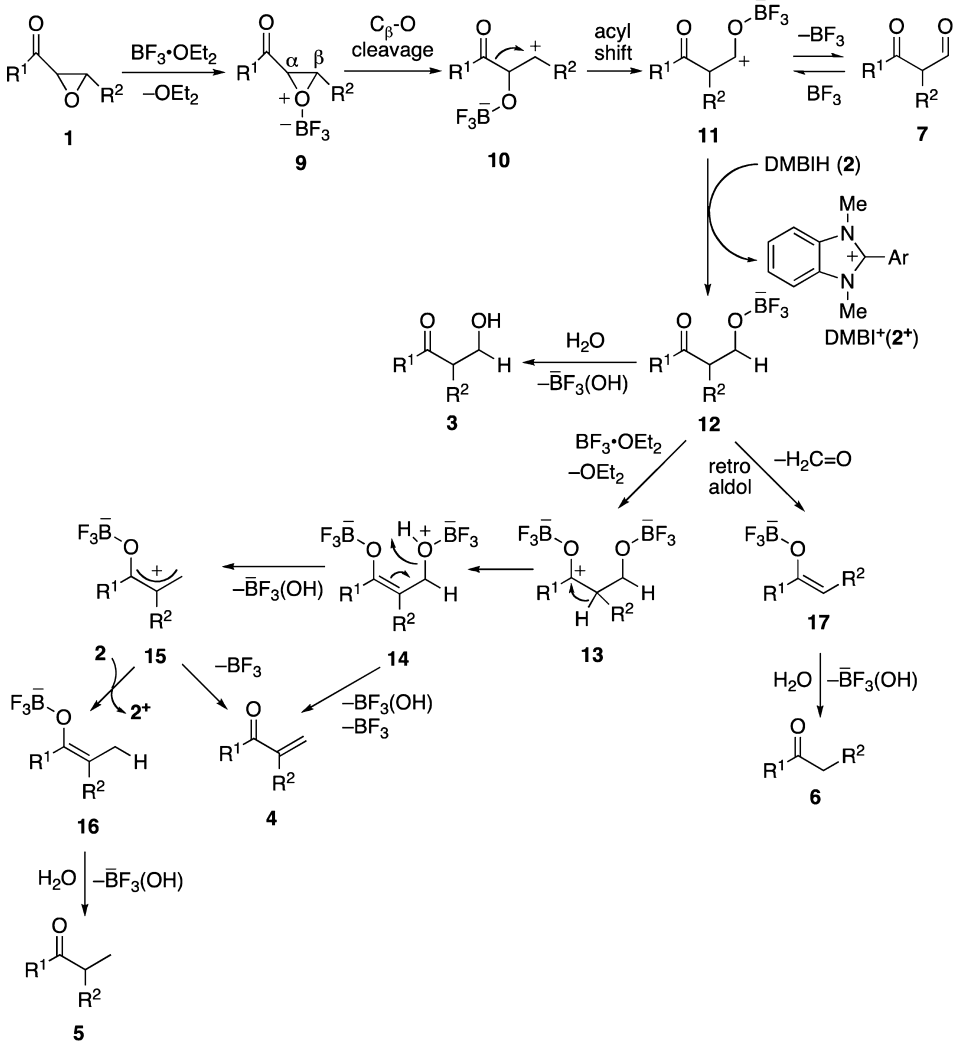
Table 3. Reactions of Various Epoxy Ketones 1 with BF_3·OEt_2 and DMBIH 2a[a]



entry	1	R^1	R^2	yield (%) 3[b]	4[c]	5[c]
1[d]	**1a**	Ph	Ph	74	1	1
2	**1b**	Ph	*p*-$MeOC_6H_4$	85	2	2
3[e]	**1c**	Ph	*p*-MeC_6H_4	69	5	5
4[e]	**1d**	Ph	*p*-ClC_6H_4	65[f]	trace[f]	1[f]
5	**1e**	Ph	1-Naph	66[f]	11[f]	0[f]
6[e]	**1f**	*p*-$MeOC_6H_4$	Ph	63	3	0
7[e]	**1g**	*p*-MeC_6H_4	Ph	66	4	1
8[e]	**1h**	*p*-ClC_6H_4	Ph	68	8	3
9	**1i**	Me	Ph	62	trace	0

[a]Conditions: **1** (0.50 mmol), BF_3·OEt_2 (1.1 equiv), **2a** (1.5 equiv), CH_2Cl_2 (1.5 mL), room temperature, 1.5 h reaction time. [b]Isolated yield. [c]Determined by using ^1H NMR. [d]Same as entry 6 in Table 1. [e]Small amounts of **6** were obtained: ca. 2% of **6c**, ca. 11% of **6d**, 3% of **6f**, 2% of **6g**, 4% of **6h**. [f]Average of two independent experiments.

Scheme 3. Plausible Reaction Pathways for Transformation of Epoxy Ketones 1 to Hydroxyl Ketones 3 and Side Products 4–6



0.6 mL of CH_2Cl_2, ca. 40 °C, 5 h) to **4a** in 88% yield (lower path in Scheme 4).[23]

These results inspired us to develop conditions for one-pot sequential transformation of **1** to **4** (Scheme 5). On the basis of

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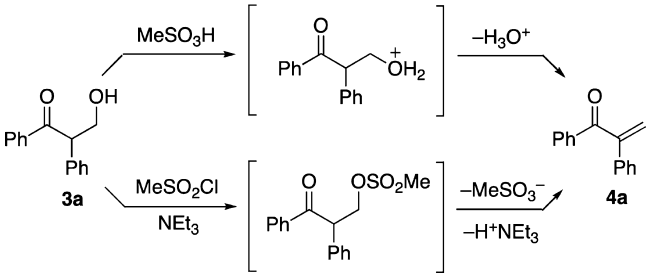
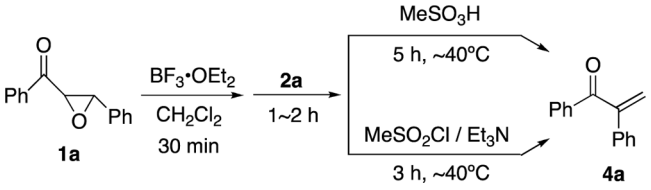
Scheme 4. Reactions of Hydroxy Ketone 3a with $MeSO_3H$ and $MeSO_3Cl$–NEt_3



Scheme 5. One-Pot Transformation of Epoxy Ketone 1a to α-Methylene Ketone 4a



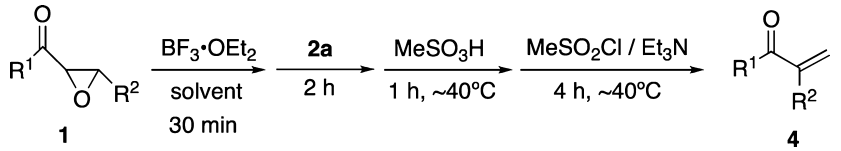
the proposed mechanism (Scheme 3), use of an excess of **2** (1.5 equiv) could cause further reduction of **4** to generate **5** when an acid is present to promote water elimination in the final step.[24] Furthermore, the reaction time (1 h) for the one-pot process was prolonged to ensure complete consumption of **2**. On the basis of this reasoning, the one-pot reaction was initiated by treatment of **1a** (0.50 mmol) with $BF_3{\cdot}OEt_2$ (1.1 equiv) for 30 min, followed by addition of **2a** (1.1 equiv) and stirring for an additional 2 h. Finally, $MeSO_3H$ (1.8 equiv) was added and the resulting mixture was stirred at ca. 40 °C for 5 h. Using this procedure (upper path in Scheme 5), **4a** was produced in 48% yield along with small amounts of **5a** (7%) and **6a** (3%). Next, we carried out the one-pot reaction using $MeSO_2Cl$ and Et_3N to induce the final water elimination step (lower path in Scheme 5). In this process, **1a** was similarly treated with BF_3OEt_2 followed by addition of **2a** (1.5 equiv) and stirring for 1 h. $MeSO_2Cl$ (1.8 equiv) and Et_3N (3.0 equiv) were added followed by heating for 1 h, further addition of Et_3N (3.0 equiv), and subsequent heating for an additional 2 h. In this case, **4a** was produced in low yield (27%) along with **6a** (6%) and a significant amount of recovered **3a** (39%).[25]

Eventually, a one-pot protocol was devised by performing a combination of the two methods described above, in which sequential processes involving rearrangement, hydride transfer, protonation and elimination proceed (Table 4).[26] The yield (63%) of **4a** (entry 2) is comparable with the overall yield of **4a** obtained using the stepwise procedure (65% derived from 74% for **1a** to **3a** and 88% of **3a** to **4a**). This one-pot sequential process was performed in other solvents using MeCN, $PhCH_3$, and $PhCF_3$ (entries 3–5) and applied to other epoxy ketones **1** (entries 6–13). The aroyl substituted α-methylene ketones **4** were obtained in modest to good yields (53–70%, entries 6–9 and 12), except for the reactions of **1f,g** affording **4f,g** in less than 50% yields (entries 10 and 11). The acetyl substituted **4i** was also obtained in low yield (entry 13). Since the yields of the corresponding aldols **3f,g,i** were similar to those of other compounds **3** (see Table 3), the relatively low yields of **4f,g,i** might be attributed to the latter steps of one-pot transformation, although this has not been confirmed yet.

CONCLUSION

In the studies described above, we demonstrated that the reagent system comprised of boron trifluoride etherate and 1,3-dimethylbenzimidazolines is effective in transforming α,β-epoxy ketones to β-hydroxy ketones. Methanesulfonic acid or methanesulfonyl chloride–triethylamine promoted dehydration of the resulting hydroxyl ketones produces α-methylene ketones. Finally, these consecutive chemical processes can be accomplished in one pot. While these compounds can be prepared by other methods,[15,20a–h] most of them require specific metal reagents, in contrast to our metal-free protocol.

Table 4. One-Pot Transformations of Epoxy Ketones 1 to Methylene Ketones 4[a]



entry	1	R^1	R^2	solvent	yield of 4 [3] (%)[b]
1[c]	**1a**	Ph	Ph	CH_2Cl_2	53 [4]
2	**1a**	Ph	Ph	CH_2Cl_2	63 [3]
3	**1a**	Ph	Ph	MeCN	47 [7]
4	**1a**	Ph	Ph	$PhCH_3$	55 [1]
5	**1a**	Ph	Ph	$PhCF_3$	54 [4]
6	**1b**	Ph	*p*-$MeOC_6H_4$	CH_2Cl_2	70 [5]
7	**1c**	Ph	*p*-MeC_6H_4	CH_2Cl_2	53 [~4]
8	**1d**	Ph	*p*-ClC_6H_4	CH_2Cl_2	55 [~8]
9	**1e**	Ph	1-Naph	CH_2Cl_2	61 [~3]
10	**1f**	*p*-$MeOC_6H_4$	Ph	CH_2Cl_2	34 [–][d]
11	**1g**	*p*-MeC_6H_4	Ph	CH_2Cl_2	46 [–][d]
12	**1h**	*p*-ClC_6H_4	Ph	CH_2Cl_2	57 [~5]
13	**1i**	Me	Ph	CH_2Cl_2	45 [0]

[a]Conditions: **1** (0.50 mmol), $BF_3{\cdot}OEt_2$ (1.1 equiv), **2a** (1.1 equiv), $MeSO_3H$ (1.8 equiv), $MeSO_2Cl$ (1.3 equiv), and Et_3N (6.0 equiv), solvent (1.5 mL). [b]Yields of **4** were determined by using ^1H NMR of the mixtures containing **6** (0–5%). Values in brackets are yields of **3**. [c]$MeSO_2Cl$ (1.8 equiv). [d]**3** was observed in the inseparable mixtures.

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Because the starting epoxy ketones are readily prepared using H_2O_2 and NaOH promoted reactions of the corresponding α,β-unsaturated ketones, the new protocol is a useful isomerization route for transforming 1,3-disubstituted 2,3-unsaturated ketones to 1,2-disubstituted 2-methylene ketones, which are synthetically useful substances. The applicability of this newly developed, metal-free, mild synthetic method will be further explored.

EXPERIMENTAL SECTION

General Considerations. NMR spectra were recorded using $CDCl_3$ solutions with tetramethylsilane (Me_4Si) as an internal standard at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR. High-resolution mass spectra (HRMS) were recorded on a double-focusing mass spectrometer by using electrospray ionization (ESI). Uncorrected melting points are reported. Column chromatography was performed using silica gel. Preparative thin-layer chromatography (TLC) was performed on 20 × 20 cm plates coated with silica gel. CH_2Cl_2 was treated with H_2SO_4, water, 5% NaOH, water, and $CaCl_2$ and then distilled over CaH_2. MeCN was distilled over P_2O_5 and subsequently distilled with K_2CO_3. Other reagents and solvents were purchased and used without further purification.

α,β-Epoxy ketones **1a**–**f**,[7b,27] **1g**,[28] **1h**,[11b,13d] and **1i**,[7b,27] which are known compounds, were prepared by reactions of the corresponding α,β-enones with H_2O_2 and NaOH according to the literature procedures.[27a] 2-Aryl-1,3-dimethylbenziimidazolines (DMBIH) **2a**,[2a,7b] **2b**,[3a] **2c**,[1] **2d**,[7e] **2e**,[7e] and **2f**[5c,7e] are known and were prepared by using reported procedures.[7e] Known products **3a**–**i**,[15] **4a**–**i**,[20] **5a**–**h**,[29] **6a**–**h**,[30] **7a**[13f] and **8a**[31] were characterized by comparison of their ^1H NMR data with those reported earlier. Spectral data were obtained for unknown compounds **3e**–**h** and **4e**.

Reaction of α,β-Epoxy Ketones 1 with $BF_3{\cdot}OEt_2$ and DMBIH 2 (Tables 1–3). *Typical Example (Entry 6 in Table 1).* To a N_2-purged CH_2Cl_2 (0.5 mL) solution containing **1a** (112 mg, 0.50 mmol) was added $BF_3{\cdot}OEt_2$ (0.07 mL, 0.56 mmol). After the mixture was stirred for 30 min, **2** (168.2 mg, 0.75 mmol) dissolved in a N_2-purged CH_2Cl_2 (1.0 mL) solution was added. The resulting mixture was stirred under N_2 at room temperature for 1 h, diluted with water, and extracted with Et_2O. The extract was washed with water and brine and dried over anhydrous $MgSO_4$. A residue obtained by the concentration of the extract in vacuo was subjected to column chromatography (EtOAc/*n*-hexane 1/5 and 2/1), giving **3a** (84 mg, 0.37 mmol, 74%). Other products, including **4a** (1 mg, 0.006 mmol, 1%) and **5a** (1 mg, 0.002 mmol, 1%), were separated by using TLC (AcOEt/*n*-hexane 1/20). Reactions of other compounds **1** and **2** were performed in a similar manner. When isolations of minor products were not performed, their yields were estimated by using ^1H NMR.

*3-Hydroxy-2-(1-naphthyl)-1-phenylpropan-1-one (**3e**):* pale yellow oil; ^1H NMR (400 MHz) δ 8.37 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.2 Hz, 2H), 7.76 (d, J = 8.4 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.34–7.25 (m, 3H), 7.14 (d, J = 7.2 Hz, 1H), 5.52 (dd, J = 3.8 Hz, J = 8.6 Hz, 1H), 4.36 (dd, J = 8.8 Hz, J = 11.6 Hz, 1H), 3.96 (dd, J = 4.0 Hz, J = 11.6 Hz, 1H), 2.63 (broad s, 1H); ^{13}C NMR (100 MHz) δ 200.6, 135.9, 134.3, 133.2, 132.0, 130.7, 129.3, 128.6, 128.5, 128.3, 127.1, 126.2, 126.0, 125.5, 122.3, 64.2, 51.9; HRMS (ESI) m/z calcd for $C_{19}H_{17}O_2$ $[M + H]^+$ 277.1218, found 277.1223.

*3-Hydroxy-1-(4-methoxyphenyl)- 2-phenylpropan-1-one (**3f**):* pale yellow oil; ^1H NMR (400 MHz) δ 7.91 (d, J = 9.5 Hz, 2H), 7.33–7.20 (m, 5H), 6.83 (d, J = 9.7 Hz, 2H), 4.73 (dd, J = 4.8 Hz, J = 8.4 Hz, 1H), 4.25 (dd, J = 9.8 Hz, J = 9.8 Hz, 1H), 3.90–3.77 (m, 3H), 2.59 (broad s, 1H); ^{13}C NMR (100 MHz) δ 198.4, 163.5, 136.6, 131.2, 129.2, 129.1, 128.3, 127.4, 113.7, 65.2, 56.0, 55.4; HRMS (ESI) m/z calcd for $C_{16}H_{16}O_3$ $(M + H)^+$ 257.1172, found 257.1167.

*3-Hydroxy-1-(4-methylphenyl)-2-phenylpropan-1-one (**3g**):* white solid; mp 53.5–56.0 °C; ^1H NMR (400 MHz) δ 7.83 (d, J = 8.4 Hz, 2H), 7.33–7.20 (m, 5H), 7.16 (d, J = 8.0 Hz, 2H), 4.76 (dd, J = 4.8 Hz, J = 8.4 Hz, 1H), 4.26 (dd, J = 8.4 Hz, J = 11.6 Hz, 1H), 3.87 (dd, J = 4.8 Hz, J = 11.6 Hz, 1H), 2.34 (s, 3H), 2.14 (broad s, 1H); ^{13}C NMR (100 MHz) δ 199.6, 144.2, 136.4, 133.7, 129.2, 129.1, 129.0, 128.4, 127.5, 65.2, 56.2, 21.6; HRMS (ESI) m/z calcd for $C_{16}H_{16}O_2Na$ $[M + Na]^+$ 263.1043, found 263.1040.

*1-(4-Chlorophenyl)-3-hydroxy-2-phenylpropan-1-one (**3h**):* white solid; mp 79.0–82.0 °C; ^1H NMR (400 MHz) δ 7.86 (d, J = 9.1 Hz, 2H), 7.36–7.22 (m, 7H), 4.72 (dd, J = 4.8 Hz, J = 8.4 Hz, 1H), 4.27 (dd, J = 8.6 Hz, J = 11.4 Hz, 1H), 3.87 (dd, J = 4.6 Hz, J = 11.4 Hz, 1H), 2.31 (broad s, 1H); ^{13}C NMR (100 MHz) δ 198.7, 139.7, 135.9, 134.5, 130.3, 129.3, 128.9, 128.3, 127.8, 65.0, 56.5; HRMS (ESI) m/z calcd for $C_{15}H_{14}{}^{35}ClO_2$ $[M + H]^+$ 261.0673, found 261.0677, calcd for $C_{15}H_{14}{}^{37}ClO_2$ $[M + H]^+$ 263.0647, found 263.0644.

*2-(1-Naphthyl)-1-phenyl-2-propen-1-one (**4e**):* white solid; mp 83.0–85.0 °C; ^1H NMR (400 MHz) d 7.97 (d, J = 7.9 Hz, 2H), 7.89–7.81 (m, 3H), 7.53 (t, J = 7.6 Hz, 1H), 7.50–7.40 (m, 6H), 6.19 (s, 1H), 6.18 (s, 1H); ^{13}C NMR (100 MHz) δ 195.6, 148.1, 137.1, 136.3, 133.6, 132.7, 131.2, 129.8, 128.8, 128.8, 128.5, 128.3, 127.3, 126.4, 125.8, 125.4, 125.1; HRMS (ESI) m/z calcd for $C_{19}H_{15}O$ $[M + H]^+$ 259.1117, found 259.1113.

Reaction of 1a with $BF_3{\cdot}OEt_2$ and Other Hydride Donors. *2,6-Dimethyl-3,5-pyridinedicarboxylate (Hanztsch Ester).* The same reaction and workup procedures as those given in entry 6 of Table 1 were performed by using **1a** (112 mg, 0.50 mmol), $BF_3{\cdot}OEt_2$ (0.07 mL, 0.56 mmol), Hantzsch ester (190 mg, 0.75 mmol), and CH_2Cl_2 (1.5 mL). Then, column chromatography (EtOAc/*n*-hexane 1/10 and 2/1) and TLC (EtOAc/*n*-hexane 1/5) were carried out. Due to the incomplete separation of **3a**, the yield of **3a** (0.14 mmol. 28%) was determined by using ^1H NMR with Ph_3CH as an internal standard. The yields of **4a** (0.018 mmol, 4%) and **7a** (0.09 mmol, 17%) were determined on the basis of the ^1H NMR signal intensities relative to that of **3a** in the crude product mixture.

Hydrosilanes (Ph_3SiH, Et_3SiH). The same reaction and workup procedure as those reported in entry 6 of Table 1 were performed by using **1a** (44.9 mg, 0.20 mmol), $BF_3{\cdot}OEt_2$ (0.03 mL, 0.24 mmol), Ph_3SiH (78.2 mg, 0.30 mmol), and CH_2Cl_2 (0.6 mL). ^1H NMR of the product mixture indicated the existence of **7a** and Ph_3SiH without other marked signals. The reaction with Et_3SiH was performed in a similar manner.

Reaction of β-Keto Aldehyde 7a with $BF_3{\cdot}OEt_2$ and DMBIH 2a (Eq 2). The same reaction and workup procedure as those reported in entry 6 of Table 1 were performed by using **7a** (112 mg, 0.50 mmol), $BF_3{\cdot}OEt_2$ (0.07 mL, 0.56 mmol), **2a** (168 mg, 0.75 mmol), and CH_2Cl_2 (1.0 mL). Column chromatography (EtOAc/*n*-hexane 1/10, 1/2, and 2/1) gave **3a** (80 mg, 0.35 mmol, 71%). Following TLC separation (AcOEt/*n*-hexane 1/20) gave **4a** (3 mg, 0.018 mmol, 3%) and **5a** (2 mg, 0.009 mmol, 2%).

Reduction of β-Keto Aldehyde 7a with $NaBH_4$ (Eq 3). To a N_2-purged MeOH (2.0 mL) solution containing **7a** (45 mg, 0.20 mmol) was added $NaBH_4$ (8 mg, 0.20 mmol). After it was stirred at room temperature for 2 h, the mixture was concentrated, diluted with water, and extracted with Et_2O. The extract was washed with water and brine and dried over anhydrous $MgSO_4$. The residue obtained by concentration of the extract in vacuo was subjected to TLC (EtOAc/*n*-hexane 1/2), giving **3a** (2 mg, 0.008 mmol, 4%), **6a** (9 mg, 0.04 mmol, 22%), and **8a** (15 mg, 0.06 mmol, 33%). Reactions of different quantities of $NaBH_4$ were similarly performed.

Transformation of β-Hydroxyl Ketone 3a to α-Methylene Ketone 4a. *Protocol using $MeSO_3H$ (Upper Path in Scheme 4).* To a N_2-purged CH_2Cl_2 (1.5 mL) solution containing **3a** (113.1 mg, 0.50 mmol) was added $MeSO_3H$ (0.03 mL, 0.46 mmol), and the resulting mixture was stirred under N_2 at 40 °C for 5 h. Then, saturated aqueous $NaHCO_3$ was added, and extraction with Et_2O was conducted. The extract was washed with water, saturated aqueous $NaHCO_3$, and brine and dried over anhydrous $MgSO_4$. Column chromatography (benzene) of the residue obtained by the concentration of the extract in vacuo gave **4a** (77 mg, 0.37 mmol, 74%).

Protocol using $MeSO_2Cl$ and NEt_2 (Lower Path in Scheme 4). To a N_2-purged CH_2Cl_2 (0.6 mL) solution containing **3a** (45 mg, 0.20 mmol) placed in an ice bath were added $MeSO_2Cl$ (0.02 mL, 0.26 mmol) and Et_3N (0.17 mL, 1.22 mmol), and the resulting mixture was stirred under N_2 at 40 °C for 5 h. The reaction mixture was diluted

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with water and extracted with Et_2O. The extract was washed with water, saturated aqueous $NaHCO_3$, and brine and dried over anhydrous $MgSO_4$. Column chromatography (benzene) of the residue obtained by the concentration of the extract in vacuo gave **4a** (37 mg, 0.18 mol, 88%).

One-Pot Transformation of α,β-Epoxy Ketones 1 to α-Methylene Ketones 4. *Protocol using $MeSO_3H$ (Upper Path in Scheme 5).* To a N_2-purged CH_2Cl_2 (0.5 mL) solution containing **1a** (112 mg, 0.50 mmol) was added $BF_3{\cdot}OEt_2$ (0.07 mL, 0.56 mmol). After the mixture was stirred for 30 min, **2** (123 mg, 0.55 mmol) dissolved in N_2-purged CH_2Cl_2 (1.0 mL) was added. The resulting mixture was stirred under N_2 at room temperature for 2 h, followed by the addition of $MeSO_3H$ (0.06 mL, 0.92 mmol). After the mixture was stirred at 40 °C for 5 h, the same workup as that used for the reaction of **3a** with $MeSO_3H$ was performed. TLC (EtOAc/*n*-hexane 1/20) of the residue obtained by the concentration of the extract in vacuo gave inseparable mixtures of **4a** and **5a** and of **4a** and **6a**. The yield of each product was determined by ^1H NMR: **4a** (0.24 mmol, 48%), **5a** (0.035 mmol, 7%), and **6a** (0.015 mmol, 3%).

Protocol using $MeSO_2Cl$–NEt_3 (Lower Path in Scheme 5). To a N_2-purged CH_2Cl_2 (0.5 mL) solution containing **1a** (112 mg, 0.50 mmol) was added $BF_3{\cdot}OEt_2$ (0.07 mL, 0.56 mmol). After the mixture was stirred for 30 min, **2** (168 mg, 0.75 mmol) dissolved in N_2-purged CH_2Cl_2 (1.0 mL) was added. The resulting mixture was stirred under N_2 at room temperature for 1 h, and then $MeSO_2Cl$ (0.07 mL, 0.90 mmol) and Et_2N (0.21 mL, 1.51 mmol) were added in an ice bath. After the mixture was stirred at 40 °C for 1 h, $MeSO_2Cl$ (0.07 mL, 0.90 mmol) and Et_3N (0.21 mL, 1.51 mmol) were added, and an additional heating at 40 °C for 2 h was performed. The same workup as used in the reaction of **3a** with $MeSO_2Cl$ and Et_3N was performed. TLC (EtOAc/*n*-hexane 1/2) of the residue obtained by the concentration of the extract in vacuo gave **3a** (44 mg, 0.20 mmol, 39%) and a mixture of **4a** and **6a**. The yields of **4a** and **6a** were determined by ^1H NMR: **4a** (0.14 mmol, 27%) and **6a** (0.14 mmol, 6%).

Sequential Treatment using $MeSO_3H$ and $MeSO_2Cl$ with NEt_3 (Table 4): Typical Example (Entry 2 in Table 4). To a N_2-purged CH_2Cl_2 (0.5 mL) solution containing **1a** (112.1 mg, 0.50 mmol) was added $BF_3{\cdot}OEt_2$ (0.07 mL, 0.56 mmol). After the mixture was stirred for 30 min, **2a** (123 mg, 0.55 mmol) dissolved in N_2-purged CH_2Cl_2 (1.0 mL) was added. The resulting mixture was stirred under N_2 at room temperature for 2 h, followed by the addition of $MeSO_3H$ (0.06 mL, 0.92 mmol). After the mixture was stirred at 40 °C for 1 h, $MeSO_3Cl$ (0.05 mL, 0.65 mmol) and Et_3N (0.42 mL, 3.01 mmol) were added in an ice bath. Then, additional heating to 40 °C for 4 h was carried out. The same workup as used in the reaction of **3a** with $MeSO_3H$ was performed. TLC (EtOAc/*n*-hexane 1/2) of the residue obtained by the concentration of the extract in vacuo gave **3a** (4 mg, 0.016 mmol, 3%) and a mixture of **4a** and **6a**. The yields of **4a** and **6a** were determined by ^1H NMR: **4a** (0.31 mmol, 63%) and **6a** (0.018 mmol, 4%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^1H NMR and ^{13}C NMR spectra of the products **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Zhu, X.-Q.; Zhang, M.-T.; Yu, A.; Wang, C.-H.; Cheng, J.-P. *J. Am. Chem. Soc.* **2008**, *130*, 2501−2516.

(2) (a) Chikashita, H.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1747−1752. (b) Chikashita, H.; Ide, H.; Itoh, K. *J. Org. Chem.* **1986**, *51*, 5400−5405. (c) Chikashita, H.; Miyazaki, M.; Itoh, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 699−706.

(3) (a) Lee, I.-S. H.; Jeoung, E. H.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1997**, *119*, 2722−2728. (b) Lee, I.-S. H.; Jeoung, E. H. *J. Org. Chem.* **1998**, *63*, 7275−7279. (c) Lee, I.-S. H.; Jeoung, E. H.; Kreevoy, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 7492−7496.

(4) Horn, M.; Schappele, L. H.; Lang-Wittkowski, G.; Mayr, H.; Ofial, A. R. *Chem. Eur. J.* **2013**, *19*, 249−263.

(5) (a) Ramos, S. M.; Tarazi, M.; Wuest, J. D. *J. Org. Chem.* **1987**, *52*, 5437−5442. (b) Benoit Bachand, B.; Ramos, S. M.; Wuest, J. D. *J. Org. Chem.* **1987**, *52*, 5443−5446. (c) Montgrain, F.; Ramos, S. M.; Wuest, J. D. *J. Org. Chem.* **1988**, *53*, 1489−1492. (d) Brunet, P.; Wuest, J. D. *Can. J. Chem.* **1996**, *74*, 689−696. (e) Schwarz, D. E.; Cameron, T. M.; Hay, P. J.; Scott, B. L.; Tumas, W.; Thorn, D. L. *Chem. Commun.* **2005**, 5919−5921.

(6) (a) Chen, J. J.; Tanner, D. D. *J. Org. Chem.* **1988**, *53*, 3897−3900. (b) Tanner, D. D.; Chen, J. J. *J. Org. Chem.* **1989**, *54*, 3842−3846. (c) Tanner, D. D.; Chen, J. J.; Chen, L.; Luelo, C. *J. Am. Chem. Soc.* **1991**, *113*, 8074−8081. (d) Tanner, D. D.; Chen, J. J.; Luelo, C.; Peters, P. M. *J. Am. Chem. Soc.* **1992**, *114*, 713−717. (e) Tanner, D. D.; Chen, J. J. *J. Org. Chem.* **1992**, *57*, 662−666.

(7) (a) Hasegawa, E.; Kato, T.; Kitazume, T.; Yanagi, K.; Hasegawa, K.; Horaguchi, T. *Tetrahedron Lett.* **1996**, *37*, 7079−7082. (b) Hasegawa, E.; Yoneoka, A.; Suzuki, K.; Kato, T.; Kitazume, T.; Yanagi, K. *Tetrahedron* **1999**, *55*, 12957−12968. (c) Hasegawa, E.; Chiba, N.; Nakajima, A.; Suzuki, K.; Yoneoka, A.; Iwaya, K. *Synthesis* **2001**, 1248−1252. (d) Hasegawa, E.; Chiba, N.; Takahashi, T.; Takizawa, S.; Kitayama, T.; Suzuki, T. *Chem. Lett.* **2004**, *33*, 18−19. (e) Hasegawa, E.; Seida, T.; Chiba, N.; Takahashi, T.; Ikeda, H. *J. Org. Chem.* **2005**, *70*, 9632−9635. (f) Hasegawa, E.; Takizawa, S.; Seida, T.; Yamaguchi, A.; Yamaguchi, N.; Chiba, N.; Takahashi, T.; Ikeda, H.; Akiyama, K. *Tetrahedron* **2006**, *62*, 6581−6588. (g) Hasegawa, E.; Hirose, H.; Sasaki, K.; Takizawa, S.; Seida, T.; Chiba, N. *Heterocycles* **2009**, *77*, 1147−1161.

(8) Feng, Y. S.; Yang, C. Y.; Huang, Q.; Xu, H. J. *Tetrahedron* **2012**, *68*, 5053−5059.

(9) (a) Tamaki, Y.; Koike, K.; Morimoto, T.; Ishitani, O. *J. Catal.* **2013**, *304*, 22−28. (b) Tamaki, Y.; Koike, K.; Morimoto, T.; Yamazaki, Y.; Ishitani, O. *Inorg. Chem.* **2013**, *52*, 11902−11909.

(10) (a) Wei, P.; Oh, J. H.; Dong, G.; Bao, Z. *J. Am. Chem. Soc.* **2010**, *132*, 8852−8853. (b) Wei, P.; Menke, T.; Naab, B. D.; Leo, K.; Riede, M.; Bao, Z. *J. Am. Chem. Soc.* **2012**, *134*, 3999−4002. (c) Wei, P.; Liu, N.; Lee, H. R.; Adijanto, E.; Ci, L.; Naab, B. D.; Zhong, J. Q.; Park, J.; Chen, W.; Cui, Y.; Bao, Z. *Nano Lett.* **2013**, *13*, 1890−1897. (d) Naab, B. D.; Guo, S.; Olthof, S.; Evans, E. G. B.; Wei, P.; Millhauser, G. L.; Kahn, A.; Barlow, S.; Marder, S. R.; Bao, Z. *J. Am. Chem. Soc.* **2013**, *135*, 15018−15025.

(11) (a) House, H. O. *J. Am. Chem. Soc.* **1956**, *78*, 2298. (b) House, H. O.; Ryerson, G. D. *J. Am. Chem. Soc.* **1961**, *83*, 979−983.

(12) (a) Bach, R. D.; Domalaga, J. M. *Tetrahedron Lett.* **1976**, *45*, 4025−4028. (b) Bach, R. D.; Klix, R. C. *Tetrahedron Lett.* **1985**, *26*, 985−988. (c) Kunisch, F.; Hobert, K.; Welzel, P. *Tetrahedron Lett.* **1985**, *26*, 6039−6042. (d) Klix, R. C.; Bach, R. D. *J. Org. Chem.* **1987**, *52*, 580−586. (e) Bach, R. D.; Klix, R. C. *J. Org. Chem.* **1985**, *50*, 5438−5440. (f) Tanaka, H.; Hiroo, M.; Ichino, K.; Ito, K. *Chem. Pharm. Bull.* **1989**, *37*, 1441−1445. (g) St. Enev, V.; Tsankova, E. T. *Tetrahedron* **1991**, *47*, 6399−6406. (h) Asaoka, M.; Hayashibe, S.; Sonoda, S.; Takei, H. *Tetrahedron* **1991**, *47*, 6967−6974. (i) Okada, K.; Katsura, T.; Tanino, H.; Kakoi, H.; Inoue, S. *Chem. Lett.* **1994**, 157−160. (j) Okada, K.; Murakami, K.; Tanino, H.; Kakoi, H.; Inoue, S. *Heterocycles* **1996**, *43*, 1735−1750. (k) Guerrab, Z.; Daou, B.; Fkih-Tetouani, S.; Ahmar, M.; Cazes, B. *Tetrahedron* **2007**, *63*, 3367−3379. (l) Wang, L. F.; Shi, Z. F.; Cao, X. P.; Li, B. S.; An, P. *Chem. Commun.* **2014**, *50*, 8061−8064. Also see a related review: (m) Cresswell, A. J.;

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Davies, S. G.; Roberts, P. M.; Thomson, J. E. *Chem. Rev.* **2014**, DOI: 10.1021/cr5001805.

(13) Similar rearrangements of epoxy ketones occur under other conditions. (a) $InCl_3$: Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212−8216. (b) $LiClO_4/Et_2O$: Sankararaman, S.; Nesakumar, J. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3173−3175. (c) Zeolites: Elings, J. A.; Lempers, H. E. B.; Sheldon, R. A. *Eur. J. Org. Chem.* **2000**, 1905−1911. (d) $Bi(OTf)_3{\cdot}xH_2O$: Bhatia, K. A.; Eash, K. J.; Leonard, N. M.; Oswald, M. C.; Mohan, R. S. *Tetrahedron Lett.* **2001**, *42*, 8129−8132. (e) Mesoporous silicate: Grieken, R. v.; Serrano, D. P.; Melero, J. A.; Garcia, A. *J. Catal.* **2005**, *236*, 122−128. (f) $AuCl_3/AgSbF_6$: Gudla, V.; Balamurugan, R. *Tetrahedron Lett.* **2012**, *53*, 5243−5247.

(14) We also discovered that similar rearrangements of epoxy ketones proceed under oxidative electron transfer conditions: Hasegawa, E.; Ishiyama, K.; Kashiwazaki, H.; Horaguchi, T.; Shimizu, T. *Tetrahedron Lett.* **1990**, *31*, 4045−4048.

(15) Representative publications of α-substituted β-hydroxy ketones. (a) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Marcantoni, E.; Sambri, L. *Chem. Eur. J.* **1998**, *4*, 2154−2161. (b) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Tetrahedron Lett.* **1999**, *40*, 2845−2848. (c) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Chem. Eur. J.* **2000**, *6*, 2590−2598. (d) Fernández-Mateos, A.; Madrazo, S. E.; Teijón, P. H.; González, R. R. *J. Org. Chem.* **2009**, *74*, 3913−3918. (e) Xu, Z. F.; Cai, C. X.; Liu, J. T. T. *Org. Lett.* **2013**, *15*, 2096−2099.

(16) Representative reviews of Hanztsch ester: (a) Eynde, J. J. V.; Mayence, A. *Molecules* **2003**, *8*, 381−391. (b) Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327−1339. (c) You, S. L. *Chem. Asian J.* **2007**, *2*, 820−827. (d) De Vries, J. G.; Mrsic, N. *Catal. Sci. Technol.* **2011**, *1*, 727−735. (e) Rueping, M.; Dufour, J.; Schoepke, F. R. *Green Chem.* **2011**, *13*, 1084−1105. (f) Zheng, C.; You, S. L. *Chem. Soc. Rev.* **2012**, *41*, 2498−2518.

(17) When CH_2Cl_2 was replaced by MeCN under the conditions shown in entry 6 of Table 1, 66% of **3a**, 2% of **4a**, and 6% of **5a** were obtained.

(18) Beauchamp, A.; Montgrain, F.; Wuest, J. D. *Acta Crystallogr., Sect. C* **1987**, *C43*, 1557−1560.

(19) Other types of substrates such as 4-methyl-1-phenyl-2,3-epoxypentan-1-one and 3,4-epoxynonan-2-one did not undergo the expected rearrangement on treatment with $BF_3{\cdot}OEt_2$. Although $BF_3{\cdot}OEt_2$ promoted rearrangement of 3,5,5-trimethyl-2,3-epoxycyclohexan-1-one (isophorone epoxide) is known,[12k] none of the expected aldol was detected with the formation of the β-keto aldehyde (~25%) under the optimized one-pot conditions.

(20) Representative examples of preparations and reactions of α-methylene ketones are as follows. Preparations: (a) Nakahira, H.; Ryu, I.; Ikebe, M.; Oku, Y.; Ogawa, A.; Kambe, N.; Sonoda, N.; Murai, S. *J. Org. Chem.* **1992**, *57*, 17−28. (b) Katritzky, A. R.; Toader, D.; Chassaing, C. *J. Org. Chem.* **1998**, *63*, 9983−9986. (c) Filho, E. P. S.; Rodrigues, J. A. R.; Moran, P. J. S. *Tetrahedron: Asymmetry* **2001**, *12*, 847−852. (d) Hon, Y. S.; Hsu, T. R.; Chen, C. Y.; Lin, Y. H.; Chang, F. J.; Hsieh, C. H.; Szu, P. H. *Tetrahedron* **2003**, *59*, 1509−1520. (e) Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566−1567. (f) Zhang, Z.; Liu, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, I. *Angew. Chem., Int. Ed.* **2010**, *49*, 1139−1142. (g) Kerr, W. J.; Morrison, A. J.; Pazicky, M.; Weber, T. *Org. Lett.* **2012**, *14*, 2250−2253. (h) Liu, J.; Yi, H.; Zhang, X.; Liu, C.; Liu, R.; Zhang, G.; Lei, A. *Chem. Commun.* **2014**, *50*, 7636−7638. Reactions: (i) Suzuki, T.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1997**, *119*, 6774−6780. (j) Koltunov, K. Y.; Walspurger, S.; Sommer, J. *Tetrahedron Lett.* **2005**, *46*, 8391−8394. (k) Fu, N.; Zhang, L.; Luo, S.; Cheng, J. P. *Chem. Eur. J.* **2013**, *19*, 15669−15681. (l) Fu, N.; Zhang, L.; Luo, S.; Cheng, J. P. *Org. Chem. Front.* **2014**, *1*, 68−72.

(21) Both H_2SO_4 in MeOH and p-$MeC_6H_4SO_3H{\cdot}H_2O$ in CH_2Cl_2 were less effective.

(22) While the use of imidazole made the reaction rather complicated, DBU was found to be less effective.

(23) Reaction at room temperature requires longer times, 70% and 77% yields of **4a** for 12 h and for 24 h, respectively.

(24) While the reaction using $MeSO_3H$ (1.0 equiv) for 5 h does not occur to completion, giving a mixture of **3a** and **4a** (**3a**/**4a** = 55/45), longer reaction times (12 h) produce **4a** along with significant amounts of **5a** (**4a**/**5a** = 73/27). On the other hand, although an increase in the quantity of $MeSO_3H$ (1.8 equiv) enables complete consumption of **3a** after 5 h, not only **4a** but also **5a** is obtained (**4a**/**5a** = 71/29). In the last case, silica gel chromatography affords 30% of **4a** and 22% of **5a** (**4a**/**5a** = 58/42), which suggests that **4a** could be partially converted to **5a** during the separation, since unreacted **2a** coexisted in the crude reaction mixture.

(25) Various conditions using different quantities of $MeSO_2Cl$ (1.3−9.7 equiv) and NEt_3 (0−10.8 equiv) for different reaction times (3−20 h) did not lead to complete consumption of **3a**. Larger quantities of $MeSO_2Cl$ and longer reaction times cause the reaction to be complicated with a lower amount of **4a** formed.

(26) In the one-pot reactions, **4** was obtained as a mixture containing small amounts of **6**. Thus, the yields of **4** were determined by using ^1H NMR, although separation of **4** from **6** is possible.

(27) (a) Hasegawa, E.; Ishiyama, K.; Horaguchi, T.; Shimizu, T. *J. Org. Chem.* **1991**, *56*, 1631−1635. (b) Hasegawa, E.; Ishiyama, K.; Kato, T.; Horaguchi, T.; Shimizu, T.; Tanaka, S.; Yamashita, Y. *J. Org. Chem.* **1992**, *57*, 5352−5359.

(28) Kumar, C. V.; Ramaiah, D.; Das, P. K.; George, M. V. *J. Org. Chem.* **1985**, *50*, 2818−2825.

(29) (a) Liu, C.; He, C.; Shi, W.; Chen, M.; Lei, A. *Org. Lett.* **2007**, *9*, 5601−5604. (b) Peng, C.; Zhang, W.; Yan, G.; Wang, J. *Org. Lett.* **2009**, *11*, 1667−1670. (c) Cheon, C. H.; Kanno, O.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 13248−13251. (d) Zhang, J.; Yang, X.; Cui, X.; Wu, Y. *Tetrahedron* **2011**, *67*, 8800−8807.

(30) (a) Nakai, H.; Imaki, K.; Okada, T.; Nakayama, Y.; Nayao, Y.; Kobayashi, K.; Sakai, Y.; Mohri, T.; Amino, T.; Kawamura, M. *Bioorg. Med. Chem.* **1996**, *4*, 2115−2134. (b) Rieke, R. D.; Suh, Y. S.; Lee, J. S.; Kim, S. H. *J. Orgnomet. Chem.* **2003**, *684*, 20−36. (c) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987−5990.

(31) Barluenga, J.; Rodríguez, F.; Vadecard, J.; Bendix, M.; Fañanás, F. J.; López-Ortiz, F. *J. Am. Chem. Soc.* **1996**, *118*, 6090−6091.

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